

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

CÔTÉ, France
Swabey Ogilvy Renault
Suite 1600
1981 McGill College Avenue
Montréal, Québec H3A 2Y3
CANADA

| | |
|---|---|
| Date of mailing (day/month/year) 23 May 2000 (23.05.00) | IMPORTANT NOTIFICATION |
| Applicant's or agent's file reference 12411-5PCT-2 | |
| International application No. PCT/CA99/00816 | International filing date (day/month/year) 07 September 1999 (07.09.99) |

1. The following indications appeared on record concerning:

☒ the applicant
 ☐ the inventor
 ☐ the agent
 ☐ the common representative

| | | |
|--|--|---------------------------------|
| Name and Address THERATECHNOLOGIES INC. 5ème Etage 630 Boulevard René-Lévesque Ouest Montréal, Québec H3B 1S6 Canada | State of Nationality CA | State of Residence CA |
| | Telephone No. (514) 877-0077 | |
| | Facsimile No. (514) 877-3177 | |
| | Teleprinter No. | |

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person
 ☐ the name
 ☒ the address
 ☐ the nationality
 ☐ the residence

| | | |
|--|--|---------------------------------|
| Name and Address THERATECHNOLOGIES INC. 2310 Alfred Nobel Blvd Saint-Laurent, Québec H4S 2A4 Canada | State of Nationality CA | State of Residence CA |
| | Telephone No. (514) 877-0077 | |
| | Facsimile No. (514) 877-3177 | |
| | Teleprinter No. | |

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

| | |
|---|---|
| <input checked="" type="checkbox"/> the receiving Office | <input type="checkbox"/> the designated Offices concerned |
| <input type="checkbox"/> the International Searching Authority | <input checked="" type="checkbox"/> the elected Offices concerned |
| <input checked="" type="checkbox"/> the International Preliminary Examining Authority | <input type="checkbox"/> other: |

| | |
|--|--|
| The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland | Authorized officer I. Britel |
| Facsimile No.: (41-22) 740.14.35 | Telephone No.: (41-22) 338.83.38 |

F ISENT COOPERATION TRE' Y

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

| | |
|--|--|
| Date of mailing (day/month/year) 02 May 2000 (02.05.00) | |
| International application No. PCT/CA99/00816 | Applicant's or agent's file reference 12411-5PCT-2 |
| International filing date (day/month/year) 07 September 1999 (07.09.99) | Priority date (day/month/year) 08 September 1998 (08.09.98) |
| Applicant GRAVEL, Denis et al | |

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
05 April 2000 (05.04.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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|---|---|
| The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35 | Authorized officer R. E. Stoffel Telephone No.: (41-22) 338.83.38 |
|---|---|

PATENT COOPERATION TRF Y

PCT

NOTIFICATION RELATING TO PRIORITY CLAIM

(PCT Rules 26bis.1 and 26bis.2 and
Administrative Instructions, Sections 402 and 409)

From the INTERNATIONAL BUREAU

To:

CÔTÉ, France
Swabey Ogilvy Renault
Suite 1600
1981 McGill College Avenue
Montréal, Québec H3A 2Y3
CANADA

| | |
|---|--|
| Date of mailing (day/month/year) 02 December 1999 (02.12.99) | IMPORTANT NOTIFICATION |
| Applicant's or agent's file reference 12411-5PCT-2 | |
| International application No. PCT/CA99/00816 | International filing date (day/month/year) 07 September 1999 (07.09.99) |
| Applicant THERATECHNOLOGIES INC. et al | |

The applicant is hereby **notified** of the following in respect of the priority claim(s) made in the international application.

1. ☒ **Correction of priority claim.** In accordance with the applicant's notice received on: **08 November 1999 (08.11.99)**, the following priority claim has been corrected to read as follows:

US 03 September 1999 (03.09.99) 09/389,486

☐ even though the indication of the number of the earlier application is missing.

☐ even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document:
2. ☐ **Addition of priority claim.** In accordance with the applicant's notice received on: , the following priority claim has been added:

☐ even though the indication of the number of the earlier application is missing.

☐ even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document:
3. ☐ As a **result of the correction and/or addition** of (a) priority claim(s) under items 1 and/or 2, the (earliest) priority date is:
4. ☐ **Priority claim considered not to have been made.**

☐ The applicant failed to respond to the Invitation under Rule 26bis.2(a) (Form PCT/IB/316) within the prescribed time limit.

☐ The applicant's notice was received after the expiration of the prescribed time limit under Rule 26bis.1(a).

☐ The applicant's notice failed to correct the priority claim so as to comply with the requirements of Rule 4.10.

The applicant may, before the technical preparations for international publication have been completed and subject to the payment of a fee, request the International Bureau to publish, together with the international application, information concerning the priority claim. See Rule 26bis.2(c) and the PCT Applicant's Guide, Volume I, Annex B2(1B).
5. ☐ In case where **multiple priorities** have been claimed, the above item(s) relate to the following priority claim(s):
6. A copy of this notification has been sent to the receiving Office and
 - ☒ to the International Searching Authority (where the international search report has not yet been issued).
 - ☒ the designated Offices (which have already been notified of the receipt of the record copy).

| | |
|--|---|
| <p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No. (41-22) 740.14.35</p> | <p>Authorized officer</p> <p style="text-align: center;">I. Britel</p> <p>Telephone No. (41-22) 338.83.38</p> |
|--|---|

PCT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

CÔTÉ, France
Swabey Ogilvy Renault
Suite 1600
1981 McGill College Avenue
Montréal, Québec H3A 2Y3
CANADA

SWABEY OGILVY RENAULT
RECEIVED
MAR 27 2000

| | | |
|--|--|--|
| Date of mailing (day/month/year) 16 March 2000 (16.03.00) | | |
| Applicant's or agent's file reference 12411-5PCT-2 | | |
| IMPORTANT NOTICE | | |
| International application No. PCT/CA99/00816 | International filing date (day/month/year) 07 September 1999 (07.09.99) | Priority date (day/month/year) 08 September 1998 (08.09.98) |
| Applicant THERATECHNOLOGIES INC. et al | | |

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
AU,CN,EP,JP,KP,KR,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CR,CU,CZ,DE,DK,DM,EA,EE,ES,FI,GB,GD,GE,GH,
GM,HR,HU,ID,IL,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,
PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZA,ZW

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
16 March 2000 (16.03.00) under No. WO 00/14236

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

| | |
|---|------------------------------------|
| The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland | Authorized officer J. Zahra |
| Facsimile No. (41-22) 740.14.35 | Telephone No. (41-22) 338.83.38 |

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | | |
|--|--|-----------|---|
| (51) International Patent Classification ⁷ : C12N 15/16, C07K 14/60, A61K 38/25, G01N 33/68 | | A3 | (11) International Publication Number: WO 00/14236 (43) International Publication Date: 16 March 2000 (16.03.00) |
| (21) International Application Number: PCT/CA99/00816 (22) International Filing Date: 7 September 1999 (07.09.99) (30) Priority Data: 09/148,982 8 September 1998 (08.09.98) US 09/389,486 3 September 1999 (03.09.99) US (71) Applicant (for all designated States except US): THERATECHNOLOGIES INC. [CA/CA]; 5ème Etage, 630 Boulevard René-Lévesque Ouest, Montréal, Québec H3B 1S6 (CA). (72) Inventors; and (75) Inventors/Applicants (for US only): GRAVEL, Denis [CA/CA]; 207 Des Pyrénées, St-Lambert, Québec J4S 1L3 (CA). HABI, Abdelkrim [CA/CA]; 7961 Champ d'Eau, Anjou, Québec H1J 1X4 (CA). BRAZEAU, Paul [CA/CA]; 4054 Avenue du Parc Lafontaine, Montréal, Québec H2L 3M8 (CA). (74) Agents: CÔTÉ, France et al.; Swabey Ogilvy Renault, Suite 1600, 1981 McGill College Avenue, Montréal, Québec H3A 2Y3 (CA). | | | (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> (88) Date of publication of the international search report: 2 June 2000 (02.06.00) |
| (54) Title: GRF ANALOGS WITH INCREASED BIOLOGICAL POTENCY (57) Abstract <p>The present invention relates to chimeric fatty body-GRF analogs with increased biological potency, their application as anabolic agents and in the diagnosis and treatment of growth hormone deficiencies. The chimeric fatty body-GRF analogs include a hydrophobic moiety (tail), and can be prepared, either by anchoring at least one hydrophobic tail to the GRF, in the chemical synthesis of GRF. The GRF analogs of the present invention are biodegradable, non-immunogenic and exhibit an improved anabolic potency with a reduced dosage and prolonged activity.</p> | | | |

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
|----|--------------------------|----|--|----|--|----|--------------------------|
| AL | Albania | ES | Spain | LS | Lesotho | SI | Slovenia |
| AM | Armenia | FI | Finland | LT | Lithuania | SK | Slovakia |
| AT | Austria | FR | France | LU | Luxembourg | SN | Senegal |
| AU | Australia | GA | Gabon | LV | Latvia | SZ | Swaziland |
| AZ | Azerbaijan | GB | United Kingdom | MC | Monaco | TD | Chad |
| BA | Bosnia and Herzegovina | GE | Georgia | MD | Republic of Moldova | TG | Togo |
| BB | Barbados | GH | Ghana | MG | Madagascar | TJ | Tajikistan |
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| BR | Brazil | IL | Israel | MR | Mauritania | UG | Uganda |
| BY | Belarus | IS | Iceland | MW | Malawi | US | United States of America |
| CA | Canada | IT | Italy | MX | Mexico | UZ | Uzbekistan |
| CF | Central African Republic | JP | Japan | NE | Niger | VN | Viet Nam |
| CG | Congo | KE | Kenya | NL | Netherlands | YU | Yugoslavia |
| CH | Switzerland | KG | Kyrgyzstan | NO | Norway | ZW | Zimbabwe |
| CI | Côte d'Ivoire | KP | Democratic People's Republic of Korea | NZ | New Zealand | | |
| CM | Cameroon | | | PL | Poland | | |
| CN | China | KR | Republic of Korea | PT | Portugal | | |
| CU | Cuba | KZ | Kazakstan | RO | Romania | | |
| CZ | Czech Republic | LC | Saint Lucia | RU | Russian Federation | | |
| DE | Germany | LI | Liechtenstein | SD | Sudan | | |
| DK | Denmark | LK | Sri Lanka | SE | Sweden | | |
| EE | Estonia | LR | Liberia | SG | Singapore | | |

INTERNATIONAL SEARCH REPORT

National Application No

PCT/CA 99/00816

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/16 C07K14/60 A61K38/25 G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K A61K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | WO 96 37514 A (THERATECHNOLOGIES INC) 28 November 1996 (1996-11-28) the whole document | 1,3-11 |
| X | MURPHY W.A. AND COY D.H.: "Potent long-acting alkylated analogs of growth hormone releasing factor." PEPTIDE RESEARCH, vol. 1, no. 1, 1988, pages 36-41, XP000877397 the whole document | 1,3-5 |
| X | US 5 112 808 A (COY DAVID H ET AL) 12 May 1992 (1992-05-12) the whole document | 1,3-6,9, 11 |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

8 March 2000

Date of mailing of the international search report

22/03/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Mandl, B

INTERNATIONAL SEARCH REPORT

ational Application No

PCT/CA 99/00816

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | US 4 914 189 A (SCHALLY ANDREW V ET AL) 3 April 1990 (1990-04-03) the whole document --- | 1,3-6,9, 11 |
| X | WO 91 16923 A (UNIV TULANE) 14 November 1991 (1991-11-14) the whole document ----- | 1,3-7, 9-11 |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA 99/00816

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 5
is directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 99/00816

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| WO 9637514 A | 28-11-1996 | AU 697119 B | 24-09-1998 |
| | | AU 5683396 A | 11-12-1996 |
| | | BR 9608799 A | 07-12-1999 |
| | | CA 2222068 A | 28-11-1996 |
| | | EP 0828758 A | 18-03-1998 |
| | | JP 11505807 T | 25-05-1999 |
| | | US 6020311 A | 01-02-2000 |
| | | US 5939386 A | 17-08-1999 |
| | | US 5861379 A | 19-01-1999 |
| US 5112808 A | 12-05-1992 | AU 613364 B | 01-08-1991 |
| | | AU 1589888 A | 17-11-1988 |
| | | DK 255688 A | 12-11-1988 |
| | | EP 0314866 A | 10-05-1989 |
| | | FI 882180 A | 12-11-1988 |
| | | IL 86102 A | 12-04-1994 |
| | | JP 2678993 B | 19-11-1997 |
| | | JP 63287799 A | 24-11-1988 |
| | | KR 136285 B | 25-04-1998 |
| | | NO 882034 A | 14-11-1988 |
| | | NZ 224487 A | 26-11-1991 |
| | | PT 87419 A, B | 31-05-1989 |
| | | ZA 8803307 A | 14-11-1988 |
| US 4914189 A | 03-04-1990 | AU 614734 B | 12-09-1991 |
| | | AU 1120388 A | 11-08-1988 |
| | | EP 0277626 A | 10-08-1988 |
| | | JP 63201198 A | 19-08-1988 |
| | | NZ 223374 A | 26-02-1991 |
| WO 9116923 A | 14-11-1991 | AU 651976 B | 11-08-1994 |
| | | AU 7882291 A | 27-11-1991 |
| | | CA 2082059 A | 05-11-1991 |
| | | EP 0527914 A | 24-02-1993 |
| | | JP 6502618 T | 24-03-1994 |

REC'D 22 DEC 2000

INFO

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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| | | |
|---|--|--|
| Applicant's or agent's file reference 12411-5PCT-2 | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) FOR FURTHER ACTION | |
| International application No. PCT/CA99/00816 | International filing date (day/month/year) 07/09/1999 | Priority date (day/month/year) 08/09/1998 |
| International Patent Classification (IPC) or national classification and IPC C12N15/16 | | |
| Applicant THERATECHNOLOGIES INC. et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 5 sheets, including this cover sheet.

- ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

| | |
|---|--|
| Date of submission of the demand 05/04/2000 | Date of completion of this report 19.12.2000 |
| Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized officer Vix, O Telephone No. +49 89 2399 7326 |



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/CA99/00816

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

Description, pages:

1-63 as originally filed

Claims, No.:

1-10 with telefax of 24/08/2000

Drawings, sheets:

1/10-10/10 as originally filed

Sequence listing part of the description, pages:

1/1, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/CA99/00816

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | | |
|-------------------------------|------|--------|------|
| Novelty (N) | Yes: | Claims | 1-10 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-10 |
| Industrial applicability (IA) | Yes: | Claims | 1-10 |
| | No: | Claims | |

- 2. Citations and explanations
see separate sheet**

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/CA99/00816

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

D1: WO 96 37514 A (THERATECHNOLOGIES INC) 28 November 1996 (1996-11-28)

D2: US-A-5 112 808 (COY DAVID H ET AL) 12 May 1992 (1992-05-12)

D3: US-A-4 914 189 (SCHALLY ANDREW V ET AL) 3 April 1990 (1990-04-03)

2. Novelty (Art. 33(2) PCT)

The present application relates to hydrophobic Growth hormone Releasing Factor (GRF) analogs with increased potency and prolonged activity and their potential application to treat growth hormone deficiencies. The problem of GRF instability and low anabolic potency was solved by anchoring an hydrophobic tail comprising a "rigidifying moiety" via an amid bond to its N-terminus in order to obtain an hydrophobic GRF analog with an increased biological potency and prolonged activity.

The exactly same approach was used and detailed in D1. However, D1 refers to chimeric fatty acid GRF analogs obtained by including an hydrophobic tail anchored to the GRF N- terminus. The GRF analog obtained exhibits an increased biological potency.

The present application differs from D1 by the addition of specific hydrophobic tails that include rigidifying substituents within the backbone (claim 1) which were not taught in D1-D3.

In summary, claims 1-10 appear to be novel over the available prior art. Therefore, said claims meet the requirements of Article 33(2) PCT.

3. Inventive step (Art. 33(3) PCT)

The subject-matter of the claims 1-10 does not appear to involve an inventive step for the following reasons:

The present application relates to hydrophobic Growth hormone Releasing Factor (GRF) analogs with increased potency and prolonged activity and their potential application of growth hormone deficiencies.

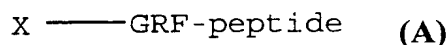
The closest prior art D1 was already faced with the problem of instability of GRF and provided chimeric fatty acid GRF analogs obtained by including a hydrophobic tail anchored to the GRF N-terminus. The GRF analog obtained exhibits an increased biological potency, being able to increase the production of growth hormone and Insulin-like Growth Factor I (IGF-I) in an animal model.

The problem to be solved by the present invention vis à vis D1 may be regarded as the provision of alternative GRF analogs with identical increased biological potency. The problem was solved by the application by using new chemical moieties that are suitable for the hydrophobic tail of the GRF analog. Such moieties do not show special new technical effects in addition to the increased potency (D1 and the present application share the exact same examples concerning the biological effects of the hexanoyl hGRF). From D2-D3 it was known that the derivatization of GRF at its N-terminus could lead to the development of more potent and longer acting analogs. More specifically, the production of GRF analogs with hydrophobic tails showing an increased potency was already taught in D1 (using tail of C5 to C7 in length as discussed in page 9 of D1). In view of D1, it would have been obvious to a person skilled in the art to arrive at the claimed subject-matter using routine methods for testing a library of hydrophobic tails to be coupled with GRF. Therefore, in absence of evidence showing unknown or unexpected effects or properties of presently claimed subject-matter, the presence of an inventive step cannot be acknowledged for the choice, testing or synthesis of further hydrophobic tails attached to the N-terminus GRF peptide.

Consequently, no inventive step can be acknowledged for the claims 1-10. Thus, these claims do not meet the requirements of Article 33(3) PCT.

WE CLAIM:

1. An hydrophobic GRF analog of formula A:



wherein;

the GRF peptide is a peptide of formula B;

A1-A2-Asp-Ala-Ile-Phe-Thr-A8-Ser-Tyr-Arg-Lys-A13-Leu-A15-Gln-Leu-A18-Ala-Arg-Lys-Leu-Leu-A24-A25-Ile-A27-A28-Arg-A30-R₀ (B)

wherein,

A1 is Tyr or His;

A2 is Val or Ala;

A8 is Asn or Ser;

A13 is Val or Ile;

A15 is Ala or Gly;

A18 is Ser or Tyr;

A24 is Gln or His;

A25 is Asp or Glu;

A27 is Met, Ile or Nle;

A28 is Ser or Asn;

A30 is a bond or any amino acid sequence of 1 up to 15 residues;

R₀ is NH₂ or NH-(CH₂)_n-CONH₂, with **n**=1 to 12 and;

X is a hydrophobic tail anchored via an amide bond to the N-terminus of the peptide and said hydrophobic tail defining a backbone of 5 to 7 atoms;

wherein said backbone can be substituted by C₁₋₆ alkyl, C₃₋₆ cycloalkyl, or C₆₋₁₂ aryl;

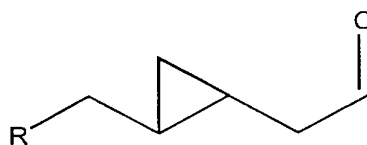
and comprises at least one rigidifying moiety connected to at least two atoms of the backbone;

said moiety selected from the group consisting of double bond, triple bond, saturated or unsaturated C₃₋₉ cycloalkyl, and C₆₋₁₂ aryl.

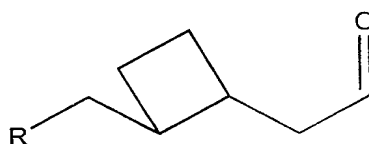
2. The hydrophobic GRF analog of claim 1, wherein X is selected from the group consisting of:



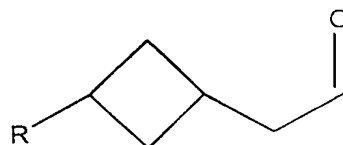
1 (R = H or CH₃ or CH₂CH₃)



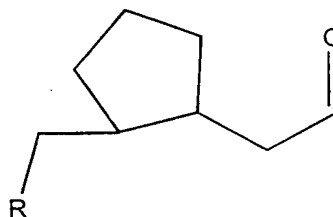
2 (R = H or CH₃ or CH₂CH₃)



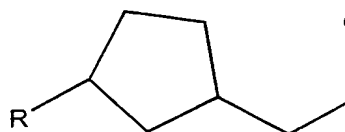
3 (R = H or CH₃ or CH₂CH₃)



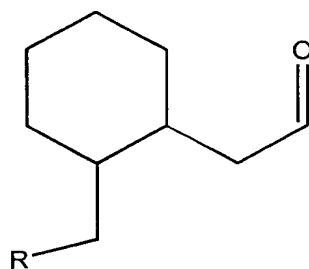
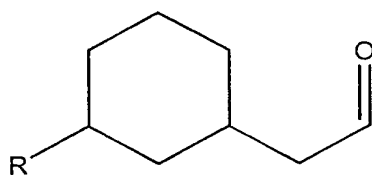
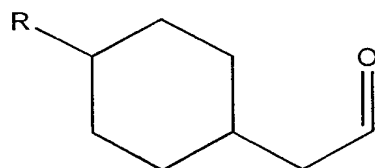
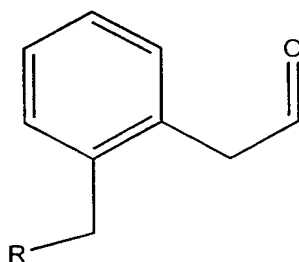
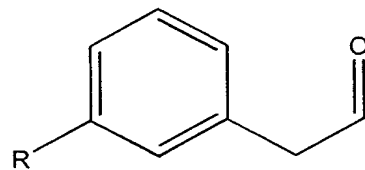
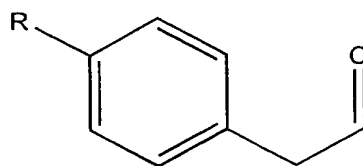
4 (R = H or CH₃ or CH₂CH₃)

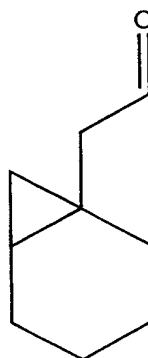


5 (R = H or CH₃ or CH₂CH₃)



6 (R = H or CH₃ or CH₂CH₃)

**7** (R = H or CH₃ or CH₂CH₃)**8** (R = H or CH₃ or CH₂CH₃)**9** (R = H or CH₃)**10** (R = H or CH₃ or CH₂CH₃)**11** (R = H or CH₃ or CH₂CH₃)**12** (R = H or CH₃)



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3. A pharmaceutical formulation for inducing growth hormone release which comprises as an active ingredient a GRF analog as claimed in claim 1, in association with a pharmaceutically acceptable carrier, excipient or diluent.
4. Use of GRF analog as claimed in claim 1 for the manufacture of a medicament for increasing the level of growth hormone in a patient which comprises administering to said patient an effective amount of said GRF analog.
5. A method for the diagnosis of growth hormone deficiencies in patients, which comprises administering to said patient a GRF analog as claimed in claim 1 and measuring the growth hormone response.
6. Use of GRF analog as claimed in claim 1 for the manufacture of a medicament for the treatment of pituitary dwarfism or growth retardation in a patient, which comprises administering to said patient an effective amount of said GRF analog.

7. Use of GRF analog as claimed in claim 1 for the manufacture of a medicament for the treatment of wound or bone healing in a patient, which comprises administering to said patient an effective amount of said GRF analog.

8. Use of GRF analog as claimed in claim 1 for the manufacture of a medicament for the treatment of osteoporosis in a patient, which comprises administering to said patient an effective amount of said GRF analog.

9. Use of GRF analog as claimed in claim 1 for the manufacture of a medicament for improving protein anabolism in human or animal, which comprises administering to said human or animal an effective amount of said GRF analog.

10. Use of GRF analog as claimed in claim 1 for the manufacture of a medicament for inducing a lipolytic effect in human or animal inflicted with clinical obesity, which comprises administering to said human or animal an effective amount of said GRF analog.

11. Use of GRF analog as claimed in claim 1 for the manufacture of a medicament for the overall upgrading of somatroph function in human or animal, which comprises administering to said human or animal an effective amount of said GRF analog.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | | |
|--|---|--|---|
| Applicant's or agent's file reference 12411-5PCT-2 | FOR FURTHER ACTION | | see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. |
| International application No. PCT/CA 99/ 00816 | International filing date (day/month/year) 07/09/1999 | (Earliest) Priority Date (day/month/year) 08/09/1998 | |
| Applicant THERATECHNOLOGIES INC. et al. | | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the abstract,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.

=

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA 99/00816

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 5
is directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

ST/CA 99/00816

IPC 7 C12N15/16 C07K14/60 A61K38/25 G01N33/68

B. FIELDS SEARCHED

IPC 7 C12N C07K A61K G01N

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | WO 96 37514 A (THERATECHNOLOGIES INC) 28 November 1996 (1996-11-28) the whole document | 1,3-11 |
| X | MURPHY W.A. AND COY D.H.: "Potent long-acting alkylated analogs of growth hormone releasing factor." PEPTIDE RESEARCH, vol. 1, no. 1, 1988, pages 36-41, XP000877397 the whole document | 1,3-5 |
| X | US 5 112 808 A (COY DAVID H ET AL) 12 May 1992 (1992-05-12) the whole document | 1,3-6,9, 11 |
| | — —/— — | |

X Patent family members are listed in annex.

"&" document member of the same patent family

Mand1. B

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 99/00816

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | US 4 914 189 A (SCHALLY ANDREW V ET AL) 3 April 1990 (1990-04-03) the whole document | 1, 3-6, 9, 11 |
| X | WO 91 16923 A (UNIV TULANE) 14 November 1991 (1991-11-14) the whole document | 1, 3-7, 9-11 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

T/CA 99/00816

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
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